REMARKS

Claims 26, 27, 29 and 30 will be pending and under consideration in the above-identified application.

Claims 31-36 have been canceled herein without prejudice. Applicants retain all rights to pursue the subject matter of the canceled claims in a related application.

Claim 26 has been amended to recite that the dose of sulodexide administered to treat diabetic nephropathy is at about 200 mg per day. Support for this amendment is found in the specification as filed, *inter alia*, at page 7, line 4 and in claim 8 as originally filed.

REJECTION UNDER 35 U.S.C. § 103(a)

Claims 26, 27 and 29-36 remain rejected under 35 U.S.C. § 103(a), allegedly, as obvious over U.S. Patent No. 5,686,432 to Baggio et al. ("Baggio") in combination with U.S. Patent No. 5,252,339 to Cristofori et al. ("Cristofori") and U.S. Patent No. 5,496,807 to Marchi ("Marchi") for reasons of record. Applicants respectfully disagree with the rejection and the Examiner's reasoning for the rejection. Applicants submit that not only has the Examiner failed to make a *prima facie* case of obviousness but also that the claimed invention exhibits surprising and unexpected results in the treatment of diabetic nephropathy.

As amended herein, the claims are directed to a method of treating a patient with diabetic nephropathy comprising orally administering to a human in need of treatment from diabetic nephropathy, an amount of sulodexide, or a pharmaceutically acceptable salt thereof, at a dose of about 200 mg/day, said amount being sufficient to decrease albumin excretion rate without causing adverse side effects. As explained in more detail below, a dosage of about 200 mg per day is the unexpected peak dosage of sulodexide in terms of efficacy and provides unexpected benefits in that the beneficial effects of sulodexide continue

even after administration has been stopped.

A rejection for obviousness is improper when there is nothing in the cited prior art references, either singly or in combination, to suggest the desirability of the claimed subject matter. For a rejection of claimed subject matter as obvious in view of a combination of prior art references to be upheld, (1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be; and (2) the prior art must have revealed that in so doing, those of ordinary skill would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). The suggestion of the claimed invention must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir 1988). Moreover, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. Rather to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). This showing of combinability must be "clear and particular". *In re Dembiczak*, 175 F.3d 994, 999; 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999).

Baggio is directed to the use of glycosaminoglycans, including sulodexide, for treating the structural and functional degradation of the peritoneal membrane in patients with renal insufficiency, such as diabetic nephropathy. Baggio states in column 2, lines 36-44 that the "therapeutically effective dosages for this treatment depend on both the glycosaminoglycan used and the kind of patient and can vary between a minimum of 20 and a maximum of 500 mg a day." (emphasis added). Applicants submit that this passage does not teach or even suggest that sulodexide can be orally administered at a dosage of about 200 mg

per day for treating diabetic nephropathy. The passage specifically states that the dosage depends on the type of glycosaminoglycan used. The passage does not state or suggest that the dosage range of sulodexide is 20 to 500 mg a day. However, Baggio does teach in column 2, line 54, that sulodexide at a dosage of 50 mg can be used. Further in Example 4, the details of which are found in columns 5 and 6, Baggio administered only 50 mg a day of sulodexide to the human patient.

Thus, Baggio, when read in its entirety as required (see, *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983)), clearly does not teach or suggest that sulodexide can be administered at a dosage of up to 500 mg a day, much less at a dosage of about 200 mg per day. Baggio clearly teaches that the dosage of the glycosaminoglycan depends on the type of glycosaminoglycan and states, in the specific case of sulodexide, that the dosage is 50 mg a day. The Examiner cannot pick and choose from among different passage in a reference or ignore certain passages, but must read the reference as a whole, in its entirety. Applicants submit that Baggio clearly does not suggest higher dosages of sulodexide.

Further, Applicants respectfully submit that the Examiner has misunderstood the teachings of Baggio with regard to what disease or organ is treated. Baggio teaches nothing about treating diabetic nephropathy or its underlying pathology in the kidney. This point is key. For even if Baggio suggested higher dosages of sulodexide, which it does not, in order for the suggestion to be relevant to the claimed invention, Baggio would need to teach the same indication as currently claimed, *i.e.*, treating diabetic nephropathy. However, Baggio merely teaches treating the peritoneal membrane of nephropathic patients undergoing peritoneal dialysis. This is a completely different indication. The peritoneal membrane is not found in the kidney, but, rather, is the membrane that lines the abdominal cavity (peritoneum) and contains the internal organs of the abdomen and pelvis, such as the stomach and large

intestine. Further, the damage to the peritoneal membrane is not due to the fact that the patient has renal insufficiency (nephropathy), but, rather, is a side-effect due to the treatment of peritoneal dialysis. Baggio teaches that the intraperitoneal administration of a glycosaminoglycan can slow or reverse the damage to the peritoneal membrane. Baggio does not teach the treatment of diabetic nephropathy, much less any other pathologic process or disease in the kidney. Moreover, no effect is taught, observed or suggested by Baggio on the underlying renal insufficiency by administration of sulodexide or of any other glycosaminoglycan. Additionally, there is no evidence that the glycosaminoglycan administered by Baggio even reaches the kidney since the intraperitoneal route of administration would not normally allow sulodexide to get into the blood stream. Therefore, Baggio provides no rationale for increasing the dosage of sulodexide to actually treat diabetic nephropathy as Baggio only teaches the treatment of a side-effect of a treatment for nephropathy. Moreover, the claim states that the amount of sulodexide administered must be sufficient to decrease the albumin excretion rate, which refers to the amount of protein in the urine of the patient. Baggio shows no change in the amount of protein excreted in the urine of the patient, only in the amount of protein in the peritoneal lavage.

Marchi does not teach a method for treating diabetic nephropathy by administering more than 150 mg sulodexide per day. In fact, Marchi administered only either (a) two capsules containing 250 LRU (25 mg) twice a day (column 3, lines 10-16 and column 4, lines 24-26 of Marchi); or (b) an injection of 600 LRU (60 mg) once a day (column 3, lines 35-40). Further, Marchi only provides evidence from clinical trials where the amounts of sulodexide administered are approximately one-fourth of the minimal amount taught and claimed in the present application. Since Marchi teaches administration of up to 150 mg per day of sulodexide, Baggio cannot fill in the gap between the prior art 150 mg to the claimed 200 mg because Baggio only teaches administering 50 mg of sulodexide for a different

purpose. As there is no relationship known in the art at the time the invention was filed between nephropathy due to diabetes and peritoneal membrane damage due to peritoneal dialysis, there is no suggestion to combine the references. The Examiner is respectfully reminded that identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. Rather there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant and this showing of combinability must be "clear and particular". *See In re Dembiczak*, 175 F.3d 994, 999; 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999).

For the same reasons, Cristofori does not fill in the gap between the claimed invention and the cited prior art. Cristofori teaches the oral administration of sulodexide but for a completely different disease, *i.e.*, the "prevention and treatment of thrombotic and atherosclerotic pathologies" (column 2, lines 50-51) and that administration of sulodexide is in such manner for "best performance of the anticoagulant, fibrinolitic antithrombotic, antitherosclerotic and antihyperlipoproteineic activities" (column 2, lines 55-58). Cristofori is completely silent as regards diabetic nephropathy, much less any kidney disease. There is no teaching or suggestion in Cristofori that has any relevance to the claimed invention. Use of a compound for one indication does not suggest its use for a wholly unrelated indication. There are no connections between the indications disclosed in Cristofori and diabetic nephropathy.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference(s) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *See, e.g., In re Mayne*, 104 F.3d 1339, 1341-42 (Fed. Cir. 1997). Third, there must be a reasonable expectation of success. A *prima facie* case of

obviousness has not been made with regard to the pending claims because there is no suggestion to combine the references since Baggio and Cristofori teach the use of sulodexide at various dosages for the treatment of a side-effect of peritoneal dialysis and prevention and treatment of thrombotic and atherosclerotic pathologies, respectively, which are completely different and are not suggestive of the treatment of diabetic nephropathy. There is simply no suggestion in the art to raise the dosage of sulodexide for treating diabetic nephropathy. Applicants respectfully submit that the Examiner has failed to make a *prima facie* case for obviousness.

In view of the foregoing remarks, Applicants respectfully submit that, as a case of *prima facie* obviousness has not been established, Applicants are not required to show new or unexpected results. However, only for the sake of argument, even if a case of *prima facie* obviousness has been established, "[o]ne way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of 'unexpected results,' *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward - that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). In the present instance, the claimed invention cannot be found to be obvious over the cited references, as administration of 200 mg of sulodexide per day provides surprising and unexpected results compared to lower and higher dosages.

The Examiner's attention is directed to the Declaration of Dr. Robert M. Niecestro under 37 C.F.R. § 1.132 ("the Rule 132 Declaration") submitted concurrently herewith. Dr. Niecestro is Vice President of Clinical and Regulatory Affairs at Keryx Biopharmaceuticals, Inc., the assignee of the present invention in the United States. According to Dr. Niecestro, patients suffering from diabetic nephropathy have been

administered 50 mg, 100 mg and 200 mg doses of sulodexide. As was expected in the art, the dose response was linear, *i.e.*, the higher the dosage the greater the efficacy. However, in only those patients administered a dose of 200 mg per day did the beneficial effect of sulodexide treatment continue for at least four months after administration of sulodexide was halted[1] (Paragraph 11 of the Rule 132 Declaration). Dr. Niecestro states that such a phenomena was unprecedented. This result alone demonstrates the nonobviousness of a dose of 200 mg per day since such a dose provided unexpected results over the prior art dosages. Applicants respectfully remind the Examiner that secondary considerations such as unexpected results must be taken into account in determining the obviousness or nonobviousness of the invention. *See e.g.*, *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). In fact, the Court of Appeals for the Federal Circuit has consistently made clear that when evidence of such secondary considerations is present, it must be considered by the Examiner or a court in determining a question of obviousness. *See e.g.*, *Stratoflex Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-39, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1983). "Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence . . . " *Stratoflex Inc. v. Aeroquip*, 713 F.2d at 1538-39, 218 U.S.P.Q. at 879. Such secondary considerations provide evidence that can both rebut a *prima facie* case of obviousness and demonstrate the nonobviousness of the claimed invention. *See e.g.*, *In re Piasecki*, 745 F.2d 1468, 223 U.S.P.Q. 785 (Fed. Cir. 1984).

Moreover, based on the previous clinical results showing a linear dose

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[1] These results are also discussed in the present specification on pages 7-9.

response, it was expected that a dose of greater than 200 mg per day would provide the same or a superior clinical benefit (Paragraph 12 of the Rule 132 Declaration). However, this was not the case when patients were administered a dose of 400 mg sulodexide per day. As explained by Dr. Niecestro in Paragraph 15 of the Rule 132 Declaration:

> The final efficacy results with the 400 mg dose of sulodexide from the Pilot Phase II study (Study KRX-101-013a) were totally unexpected. It was hypothesized prior to the initiation of Study KRX-101-013a that the 400 mg dose of sulodexide would be at least equal to or superior to the 200 mg dose. The finding in Study KRX-101-013a that the 400 mg was less efficacious, no further dose-response was documented, no plateau in the dose-response was observed with a 400 mg dose, and a decrease in the efficacy of the 400 mg as compared to the 200 mg was unexpected and clearly demonstrates that a dose of approximately 200 mg of sulodexide represents the best dose for the treatment of diabetic nephropathy. Increasing the dose of sulodexide from 200 mg to 400 mg with no increase in the efficacy of sulodexide was totally unexpected. The following findings regarding the efficacy of the 400 mg dose of sulodexide were totally unexpected:
>
> 1. The 400 mg dose was less efficacious in normalizing micro-albuminuria and was therefore less effective than 200 mg.
>
> 2. The 400 mg dose was less efficacious in reducing ACR by > 50% as compared to 200 mg.
>
> 3. The average change in ACR versus baseline over time was different between the 200 and 400 mg dose of sulodexide. Based on a review of the data, the 400 mg dose of sulodexide never reduced ACR; while the 200 mg dose of sulodexide clearly reduced ACR. This finding was unexpected.
>
> 4. In the eight small Pilot II studies, the DiNAS study, and with the 200 mg dose of sulodexide in KRX-101-013a study, the effects of sulodexide on lowering either ACR or AER were seen approximately two to four months off therapy, while the 400 mg dose of sulodexide in Study KRX-101-013 did not show a similar prolonged effect. This finding was never anticipated and clearly shows that the 400 mg dose of sulodexide is working fundamentally different than the 200 mg in terms of restoring the anionic charge of the glomerular basement membrane.

Dr. Niecestro concludes that "[i]n view of the unexpected results of the 200 mg dose of sulodexide providing long term reduction in AER as compared to the 100 mg dose and the fact that the 400 mg dose of sulodexide was less efficacious that the 200 mg

dose, it is my opinion that a dose of about 200 mg per day of sulodexide for the treatment of diabetic nephropathy is a peak dosage for sulodexide in which dosages higher and lower have been shown to have less efficacy. The fact that sulodexide has a peak dosage is wholly unexpected in view of the results of the clinical trials in which 50 mg, 100 mg or 200 mg had been given as the dose response in those studies was linear, *i.e.*, the higher the dose, the greater the efficacy."

Therefore, in view of the foregoing, Applicants respectfully submit that presently claimed invention provides unexpected results, which evidences the nonobviousness of the claimed invention. Therefore, the Section 103 rejection is improper, and Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants respectfully request that the remarks of the present response be entered and made of record in the present application. Claims 26, 27 and 29-30 fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejection and allowance and action for issuance are respectfully requested.

Applicants request that the Examiner call the undersigned at (212) 326-3921 if any questions or issues remain.

Respectfully submitted,

Date: September 27, 2006

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